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CERTIFICATE

This certificate is issued in support of an application for Patent registration in a country outside New Zealand pursuant to the Patents Act 1953 and the Regulations thereunder.

I hereby certify that annexed is a true copy of the Provisional Specification as filed on 19 July 2002 with an application for Letters Patent number 520295 made by Ashmont Holdings Limited.

Dated 6 August 2003.

Neville Harris
Commissioner of Patents

Patents Form # 4

520295

NEW ZEALAND

Patents Act 1953

PROVISIONAL SPECIFICATION

Title: ANTHELMINTIC FORMULATIONS

We. ***ASHMONT HOLDINGS LIMITED,***
Nationality: *A New Zealand company*
Address: *First Floor, 17 Shea Terrace, Takapuna, Auckland, New Zealand,*
do hereby declare this invention to be described in the following statement :

FIELD OF THE INVENTION

This invention relates to the field of veterinary pharmaceuticals and in particular to formulation including a combination of actives.

BACKGROUND

Anthelmintics are an important tool for farmers seeking to improve the productivity of grazing cattle. The first class of modern broad-spectrum anthelmintic was the benzimidazoles introduced in the early 1960's, followed by the levamisole/morantel class in the late 1960's and finally the avermectin/milbemycin class in the early 1980's.

Unfortunately parasite resistance has now been reported to all 3 classes of chemical. Resistance to benzimidazole based drenches is widespread throughout the world. Cases have been reported that involve all the three major cattle parasites, *Ostertagia*, *Trichostrongylus* and *Cooperia*.

Resistance to levamisole is present but is much less widespread than benzimidazole resitance.

In 1995 NZ researchers reported a strain of *Cooperia* that was resistant to both ivermectin (a member of the avermectin/milbemycin class) and oxfendazole (a benzimidazole based drench). In 1996 reports were published of an ivermectin resistant *Cooperia* strain that was cross-resistant to doramectin and moxidectin (other members of the avermectin/milbemycin class).

To prevent and manage the problem of drench resistance farmers have used a number of strategies including:

- minimizing anthelmintic use by only treating at strategically important times
- alternating the class of anthelmintic used

A further strategy has been using combinations of chemicals from different classes to reduce the potential of parasites to survive the treatment.

Combinations of benzimidazole and levamisole active are well known, and have been used for many years.

In recent times avermectin/milbemycin chemicals have held a majority share of the market due to their high efficacy against the major production parasite species, *Ostertagia*. The availability of easy to apply topical formulations of avermectin/milbemycin chemicals has further extended their market dominance. Levamisole on the other hand is used on a much more limited basis, despite its good efficacy against *Cooperia*, the key dose limiting parasite of the avermectin/milbemycin class. The table below shows that while each class has particular limitations against certain parasites, a combination of both would achieve a double set of highly important goals:

- high efficacy against the key cattle parasites
- combination benefits in reducing the potential for resistance

Chemical Class	*Cooperia* Efficacy	*Ostertagia* Efficacy
Levamisole/Morantel	Good	Poor
Avermectin/Milbemycin	Poor	Good
Combination of both classes	Good	Good

Despite the rationale for a product combining a levamisole/morantel active with an avermectin/milbemycin active, and the long period since the introduction of both chemical classes, there have been no such combination products developed for cattle.

Particularly it would be of great benefit if farmers could have access to a combination product that combined high efficacy, stability and ease of use.

This lack of availability has much to do with the difficulty of combining the avermectin/milbemycin (water insoluble) and levamisole/morantel (water soluble) actives together, in a formulation that is compatable and stable. To make this problem even more difficult levamisole requires a pH of less than 4, whilst avermectin/milbemycin requires a pH of approx. 6.6.

In addition to the stability issues test formulations for topical application including levamisole and avermectin/milbemycin have given rise to gross skin irritation at the site of application.

Accordingly there is a need for a new formulation capable of stably integrating both avermectin or milbemycin together with levamisole.

OBJECT

It is an object of the present invention to provide an improved formulation or one that will at least provide the public with a useful choice.

STATEMENTS OF INVENTION

In one aspect the invention relates to a stable formulation suitable for administration to animals including at least 2 actives wherein a first of the actives is selected from the group including avermectins and milbemycins and the second of said actives is levamisole, said actives being dissolved in a solvent selected from the group including pyrrolidones.

Preferably the avermectin or milbemycin is selected from the group including abamectin, doramectin, eprinomectin, ivermectin and moxidectin.

More preferably the avermectin or milbemycin is present in the range of between 0.01 – 5% w/v.

Preferably levamisole is present in the range of between 1 – 30% w/v.

Preferably the formulation additionally includes at least one further medicament selected from the group anthelmintics, dietary supplements, vitamins, mineral and other beneficial agents.

More preferably wherein the formulation additionally includes excipients including preservatives, stabilisers, flavorants, co solvents.

More preferably the formulation is suitable for topical administration. However in the alternative it maybe administered by injection or orally.

Most preferably where topical administration is preferred the formulation does not cause unacceptable levels of irritancy.

In a further related aspect the invention relates to a method of treating or preventing infection of cattle with Cooperia or Ostertagia by administering a formulation of the present invention.

DESCRIPTION

Summary of Stability Studies conducted on Levamisole base & Abamectin Pour on formulations

A large number of studies were undertaken over a 3 year period to develop a stable formulation of levamisole or morantel when mixed with an avermectin or milbemycin based active ingredient. In the studies abamectin was used as the representative avermectin/milbemycin active, whilst levamisole in its base form was used as the representative levamisole/morantel active.

Study 1

1. Formulations

	R20	R27	R28	R29	Ivomec®	Levipor ®	Ivomec® Plus injection
Lev.base	20.0 g	20.0 g	20.0 g	20.0 g	--	20.0 g	--
Abamectin	1.0 g	1.0 g	1.0 g	1.0 g	--	--	--
Ivermectin	--	--	--	--	0.5 g	--	3.0 g
Lev.phos	--	--	--	--	--	--	--
Propylene Glycol	50 g	41 g	50 g	41 g			
Benzyl alcohol	--	--	10 g	10 g			
BHT	0.2 g	0.2 g	0.2 g	0.2 g			
IPA	--	4 g	--	4 g			
*DGMEE to	100ml	100ml	100ml	100ml	* No more details		

*DGMEE: Diethylene glycol monoethyl ether (Transcutol ®)

2. Stability results

		0 day	5d /60°C	10d /60°C	15d /60°C	20d /60°C	25d /60°C	Light /25°C	Dark /25°C
R20	Lev.base	100%	93.1%	92.0%	88.4%	84.9%	83.2%	92.0%	92.0%
	Aba	100%	86.2%	84.0%	66.3%	26.9%	5.4%	94.6%	96.7%
R27	Lev.base	100%	88.1%	83.6%	83.8%	83.2%	79.9%	83.9%	88.2%
	Aba	100%	80.7%	78.5%	67.0%	58.5%	37.6%	85.6%	90.7%
R28	Lev.base	100%	85.7%	82.1%	82.7%	79.5%	75.3%	83.3%	88.7%
	Aba	100%	84.5%	84.2%	76.5%	73.5%	60.9%	93.6%	97.2%
R29	Lev.base	100%	88.3%	85.6%	88.3%	85.2%	81.3%	83.1%	91.3%
	Aba	100%	92.2%	92.3%	85.9%	84.2%	84.5%	91.5%	93.5%
Ivomec ®	Ivermectin	100%	99.9%	--*	--*	--*	--*	97.8%	96.6%
Levipor ®	Lev.base	100%	82.0%	--*	--*	--*	--*	89.3%	89.7%
Ivermec ® plus injection	Ivermectin	100%	97.9%	93.1%	91.7%	95.9% (?)	90.7%	31.3%	95.8%

*: solvent evaporated

3. Discussion and conclusion

1) Abamectin degraded more quickly than the Levamisole base component did. The stability of abamectin should be considered as the main factor.

2) R29 was viewed as a relatively hopeful formulation.

Study 2

1. Formulation

Ingredients	Concentration (%, w/v)					
	029/0	029/1	029/2/BHT	029/3/BHT	029/4/BHA	029/5/BHA
Lev.base	20.0	20.0	20.0	20.0	20.0	20.0
Abamectin	1.0	1.0	1.0	1.0	1.0	1.0
Propylene Glycol	41.0	41.0	41.0	41.0	41.0	41.0
Benzyl Alcohol	--	15.0	15.0	15.0	15.0	15.0
Isopropyl myristate	4.0	4.0	4.0	4.0	4.0	4.0
BHT	--	--	0.2	1.0	--	--
BHA	--	--	--	--	0.2	1.0
Diethylene glycol monoethyl ether to	100ml	100ml	100ml	100ml	100ml	100ml

2. pH value (BA350 pH Meter)

	0 day	5d /60°C	10d /60°C	15d /60°C	20d /60°C	25d /60°C	30d /60°C	1 Month /37°C	2 Month /37°C	3 Month /37°C
029/0	8.81	9.05 (+0.24)	9.18 (+0.37)	9.18 (+0.37)	9.11 (+0.30)	9.13 (+0.32)	9.21 (+0.40)	8.90 (+0.09)	8.95 (+0.14)	8.46 (-0.35)
029/1	9.02	9.15 (+0.13)	9.21 (+0.19)	9.22 (+0.20)	9.19 (+0.17)	9.26 (+0.24)	9.25 (+0.23)	9.05 (+0.03)	9.05 (+0.03)	8.47 (-0.55)
029/2/BHT	9.13	9.09 (-0.04)	9.11 (-0.02)	9.30 (+0.17)	9.26 (+0.13)	9.32 (+0.19)	9.23 (+0.10)	9.08 (-0.05)	9.06 (-0.07)	8.47 (-0.66)
029/3/BHT	9.15	9.15 (0)	9.18 (+0.03)	9.21 (+0.06)	9.22 (+0.07)	9.26 (+0.11)	9.19 (+0.04)	9.08 (-0.07)	9.05 (-0.10)	8.50 (-0.65)
029/4/BHA	9.05	9.04 (-0.01)	9.09 (+0.04)	9.20 (+0.15)	9.04 (-0.01)	9.13 (+0.08)	9.11 (+0.06)	9.00 (-0.05)	8.99 (-0.06)	8.48 (-0.57)
029/5/BHA	9.03	9.02 (-0.01)	9.06 (+0.03)	9.11 (+0.08)	9.18 (+0.15)	9.08 (+0.05)	9.19 (+0.16)	9.00 (-0.03)	9.06 (+0.03)	8.54 (-0.49)
Ivomec®	5.05	5.09 (+0.04)	5.01 (-0.04)	4.96 (-0.09)	5.10 (+0.05)	5.04 (-0.01)	4.96 (-0.09)	4.76 (-0.29)	4.94 (-0.11)	4.48 (-0.57)
Levipor®	7.59	8.60 (+1.01)	8.76 (+1.17)	8.80 (+1.21)	8.56 (+0.97)	8.68 (+1.09)	8.75 (+1.16)	8.00 (+0.41)	8.24 (+0.65)	8.15 (0.56)

3. Stability results

		0 day	20d /60°C	25d /60°C	30d /60°C	1 Month /37°C	2 Month /37°C	3 Month /37°C
029/0	Lev.base	100%	91.0%	90.1%	88.2%	95.0%	100.9% (?)	ND
	Aba	100%	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	ND
029/1	Lev.base	100%	76.3%	78.7%	75.1%	96.3%	89.4%	ND
	Aba	100%	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	ND
029/2/BHT	Lev.base	100%	83.2%	74.4%	70.9%	95.4%	103.5% (?)	ND
	Aba	100%	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	ND

029/3/BHT	Lev.base	100%	84.1%	78.1%	70.2%	96.8%	90.8%	ND
	Aba	100%	76.2%	56.1%	12.5%	96.2%	50.2%	ND
029/4/BHA	Lev.base	100%	82.8%	73.6%	73.2%	96.9%	91.7%	ND
	Aba	100%	76.7%	54.5%	14.9%	96.2%	51.0%	ND
029/5/BHA	Lev.base	100%	85.0%	77.9%	74.5%	100.4%	94.1%	ND
	Aba	100%	77.8%	56.2%	13.0%	100.0%	55.2%	ND
Ivomec®	Iver	100%	95.0%	98.0%	101.3%	100.3%	100.3%	ND
Levipor®	Lev.base	100%	102.0%	102.9%	100.9%	104.5%	94.9%	ND

4. Discussion and conclusion

1) Benzyl alcohol is not a good solvent for the stability of lev.base (compare 029/0 and 029/1). even though it is very good for solubilising abamectin.

2) BHT or BHA did not have a benefit in improving the stability of the actives.

Study 3

1. Formulation (052901)

	R 1	R 2	R 3	R 4
Levamisole base	20.0 g	--	20.0 g	20.0 g
Abamectin	--	1.0 g	1.0 g	1.0 g
Propylene glycol	to 100 ml	--	--	40 ml
*DGBE to		100 ml	100 ml	100 ml

*DGBE: Diethylene glycol n-butyl ether (Butyl carbitol®)

		R 5	R 6
Part 1	Levamisole base	10.0 g	10.0 g
	Propylene glycol	33 ml	--
	Isopropyl myristate	4 ml	--
	DGMBE to	90 ml	90 ml
Part 2	Abamectin	0.5 g	0.5 g
	Benzyl alcohol	2 ml	2 ml
	Propylene glycol to	10 ml	10 ml

2. Stability results

		0 day	5 d/60°C	10 d/60°C	15 d/60°C	20 d/60°C
R1 (Lev.base)		100%	101.4%	104.9%	100.3%	105.8%
R5-1 (Lev.base)		100%	97.2%	100.8%	97.9%	99.9%
R6-1 (Lev.base)		100%	103.2%	101.5%	105.2%	98.0%
R2 (Aba)		100%	88.4%	82.5%	82.5%	81.5%
R5-2 (Aba)		100%	82.6%	78.4%	76.9%	62.9%
R3	Lev.base	100%	98.2%	99.0%	104.3%	100.5%
	Aba	100%	73.5%	67.5%	60.0%	52.8%
R4	Lev.base	100%	96.6%	100.6%	89.3%	95.5%
	Aba	100%	67.8%	62.6%	55.5%	33.4%

3. Discussion and conclusion

1) Levamisole base is very stable in all formulations, whether alone or combination.

2) Abamectin degraded in all formulations, whether alone or combination, but the degradation speed was different in different formulations.

*abamectin degraded more quickly when it was combined with levamisole base than when it was alone.

*abamectin degraded more quickly in R4 than in R3, which hinted that propylene glycol is not a good solvent for the stability of abamectin.

*abamectin degraded more quickly in R5-2 than in R2, which hinted that maybe DGBE is a relatively good solvent for abamectin.

3) Propylene glycol is a relatively good solvent for levamisole base (R5-1).

4) Glycerin formal is a relatively good solvent for abamectin

Study 4

1. Formulation (BN: 070701)

	1%Abamectin			20%Lev.base		1%Aba+20%Lev.base		
	1-1	1-2	1-3	2-1	2-2	3-1	3-2	3-3
Aba	1.0 g	1.0 g	1.0 g	--	--	1.0 g	1.0 g	1.0 g
Leva.base	--	--	--	20.0 g	20.0 g	20.0 g	20.0 g	20.0 g
BHT	--	0.2 g	2.0 g	--	0.2 g	--	0.2 g	2.0 g
*DGBE to	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

*DGBE: Diethylene Glycol n-butyl Ether

2. pH value (BA350 pH Meter)

	0 day	10 days/60°C	20 days/60°C	30 days/60°C
1-1	6.28	5.40 (-0.88)	5.24 (-1.04)	5.20 (-1.08)
1-2	5.35	5.24 (-0.11)	5.16 (-0.19)	5.05 (-0.30)
1-3	5.38	5.16 (-0.22)	5.91 (0.53)(?)	5.19 (-0.19)
2-1	8.20	8.52 (0.32)	8.68 (0.48)	8.34 (0.14)
2-2	8.30	8.53 (0.23)	8.76 (0.46)	8.44 (0.14)
3-1	8.23	8.45 (0.22)	8.69 (0.46)	8.37 (0.14)
3-2	8.22	8.46 (0.24)	8.69 (0.47)	8.30 (0.08)
3-3	8.23	8.44 (0.21)	8.70 (0.47)	8.39 (0.16)

3. Stability results

		0 days	10days/60°C	20days/60°C	30days/60°C
1-1	Aba	100%	106.2%	103.8%	76.0%
1-2	Aba	100%	108.1% (?)	110.1% (?)	110.5% (?)
1-3	Aba	100%	102.6%	101.8%	101.0%
2-1	Lev.base	100%	96.1%	98.1%	89.5%
2-2	Lev.base	100%	97.8%	100.3%	96.7%
3-1	Lev.base	100%	94.2%	96.7%	92.8%
	Aba	*100%*	*[illegible]*	*[illegible]*	*[illegible]*
3-2	Lev.base	100%	96.8%	97.9%	91.5%
	Aba	*100%*	*[illegible]*	*[illegible]*	*[illegible]*
3-3	Lev.base	100%	98.0%	91.1%	89.6%
	Aba	*100%*	*[illegible]*	*[illegible]*	*[illegible]*

4. Discussion and conclusion

1) BHT or BHA showed some active effect for retarding the degradation of lev.base or abamectin alone, but had no marked effect on the stability of lev.base & abamectin Pour On.

2) Some data was inconsistent.

Study 5

1. Formulation (BN: 260701)

	029/0 - 1	029/0 - 2	029/0 - 3
Lev.base	20.0 g	20.0 g	20.0 g
Abamectin	1.0 g	1.0 g	1.0 g
Propylene glycol	41 ml	41 ml	41 ml
Isopropyl mysristate	4.0 ml	4.0 ml	4.0 ml
BHT/BHA	-	BHT 0.2 g	BHA 0.2 g
*DGMEE to	100 ml	100 ml	100 ml

*DGMEE: Diethylene glycol monoethyl ether

2. pH value (BA350 pH Meter)

	0 day	10d/60°C	20d/60°C	30d/60°C
029/0-1	8.78	8.73 (-0.05)	8.82 (0.04)	ND
029/0-2	8.76	8.74 (-0.02)	8.80 (0.04)	ND
029/0-3	8.75	8.74 (-0.01)	8.81 (0.06)	ND

3. Stability results

		0 day	10d/60°C	20d/60°C	30d/60°C
029/0-1	Lev.base	100%	94.5%	86.2%	ND
	Aba	100%	96.1%	70.1%	ND
029/0-2	Lev.base	100%	97.3%	80.6%	ND
	Aba	100%	97.0%	78.7%	ND
029/0-3	Lev.base	100%	94.9%	91.5%	ND
	Aba	100%	89.6%	73.6%	ND

4. Discussion and conclusion

1) BHT or BHA had a marked effect of retarding the degradation of abamectin

2) BHA had a marked effect for retarding the degradation of lev.base.

Study 6

1. Formulation (BN: 121001)

	R1	R2	R3	R4	R5	R6
Lev.base	20.0 g	20.0 g	20.0 g	20.0 g	20.0 g	20.0 g
Abamectin	1.0 g	1.0 g	1.0 g	1.0 g	1.0 g	1.0 g
BHT	--	--	--	0.2 g	0.2 g	0.2 g
Benzoic acid	--	0.05 g	0.2 g	--	0.05 g	0.2 g
*DGBE to	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

*DGBE: Diethylene Glycol n-butyl Ether

2. Stability results (Mobile phase: ACN-H_2O-Ammonia: 80:20:0.1,V/V)

		0 day	10d /60°C	20d /60°C	30d /60°C	1 Month /37°C	2 Month /37°C	3 Month /37°C
R1	Lev.base	100%	100.4%	98.9%	99.0%	98.7%	98.2%	98.6%
	Aba	100%	65.2%	46.2%	42.3%	88.4%	72.0%	56.6%
R2	Lev.base	100%	99.4%	98.7%	98.6%	97.9%	97.3%	96.6%
	Aba	100%	59.2%	42.0%	36.6%	79.4%	62.7%	56.6%
R3	Lev.base	100%	100.2%	103.2%	101.3%	102.4%	101.2%	102.4%
	Aba	100%	66.3%	59.1%	44.1%	85.3%	73.9%	62.8%
R4	Lev.base	100%	100.1%	98.7%	99.5%	100.2%	101.1%	100.2%
	Aba	100%	67.5%	52.2%	47.1%	93.8%	62.2%	55.2%
R5	Lev.base	100%	99.6%	99.1%	98.4%	99.2%	98.9%	99.5%
	Aba	100%	62.1%	39.0%	27.8%	79.0%	61.7%	55.2%
R6	Lev.base	100%	100.1%	100.7%	99.2%	103.4%	101.2%	101.1%
	Aba	100%	53.5%	49.7%	39.9%	88.6%	62.1%	47.7%

3. Discussion

1) The stability of Abamectin showed no improvement with 0.05% or 0.2%Benzoic acid in the formulation.

2) The stability of Abamectin showed no improvement with 0.05% or 0.2%BHT in the formulation.

Study 7 (Solubility of actives & additives and Formulation)

1. Solubility of actives & additives

1.1 Solubility of actives

	Lev.base (1g)	Lev.phos(0.2g)	Lev.HCl (0.2g)	Aba (0.05g)
1)Propylene Glycol	1ml (clear) (>100%)	2ml (clear) (>10%)	3ml (clear) (>6.7%)	7ml (clear) (>0.7%)
2)Benzyl alcohol	0.5ml (clear) (>200%)	2ml (clear) (>10%)	1ml (clear) (>20%)	0.2ml (clear) (>25%)
3)Glycerin Formal	0.5ml (clear) (>200%)	2ml (clear) (>10%)	1ml (clear) (>20%)	0.5ml (clear) (>10%)
4)Diethylene glycol monoethyl ether (DGMEE)	1ml (clear) (>100%)	10ml (unclear) (<2%)	10ml (unclear) (<2%)	1ml (clear) (>5%)
5)Diethylene glycol n-butyl ether (DGBE)	1ml (clear) (>100%)	10ml (unclear) (<2%)	10ml (unclear) (<2%)	1ml (clear) (>5%)
6)Capmul MCM	1ml (clear) (>100%)	5ml (clear) (>4%)	6ml (clear) (>3.3%)	2ml (clear) (>2.5%)
7)Isopropyl alcohol (IPA)	0.5ml (clear) (>200%)	10ml (unclear) (<2%)	10ml (clear) (>2%)	1ml (clear) (>5%)
8)Isopropyl Myristate	20ml (unclear) (<5%)	10ml (unclear) (<2%)	10ml (unclear) (<2%)	10ml (unclear) (<0.5%)
9)Dipropylene glycol methyl ether (DPM)	1ml (clear) (>100%)	10ml (unclear) (<2%)	10ml (unclear) (<2%)	1ml (clear) (>5%)

1.2 Solubility of actives

	2.5 mol/L HCl (0.5ml)	Benzoic acid (0.1g)	Vitc (0.1g)	Citric acid (0.1g)	Succinic acid (0.1g)	Mannitol (0.1g)
1)Propylene Glycol	1ml (clear) (pH1.0)	2ml (clear) (>5%)	20ml (unclear) (<0.5%)	3ml (clear) (>3.3%)	8ml (clear) (>1.25%)	20ml (unclear) (<0.5%)
2)Benzyl alcohol	5ml (clear) (pH1.0)	1ml (clear) (>10%)	25ml (unclear) (<0.4%)	3ml (clear) (>3.3%)	10ml (clear) (>1%)	15ml (unclear) (<0.67%)
3)Glycerin Formal	1ml (clear) (pH1.0)	1ml (clear) (>10%)	20ml (clear) (>0.5%)	5ml (clear) (>2%)	5ml (clear) (>2%)	15ml (unclear) (<0.67%)
4)Diethylene glycol monoethyl ether	0.5ml (clear) (pH1.0)	1ml (clear) (>10%)	20ml (unclear) (<0.5%)	3ml (clear) (>3.3%)	8ml (clear) (>1.25%)	20ml (unclear) (<0.5%)

(DGMEE)						
5)Diethylene glycol n-butyl ether (DGBE)	0.5ml (clear) (pH1.0)	1ml (clear) (>10%)	20ml (unclear) (<0.5%)	3ml (clear) (>3.3%)	10ml (clear) (>1%)	20ml (unclear) (<0.5%)
6)Capmul MCM	5ml (clear) (pH1.0)	3ml (clear) (>3.3%)	25ml (unclear) (<0.4%)	15ml (unclear) (<0.7%)	20ml (unclear) (<0.5%)	15ml (unclear) (<0.67%)
7)Isopropyl alcohol (IPA)	1ml (clear) (pH1.0)	1ml (clear) (>10%)	25ml (unclear) (<0.4%)	1ml (clear) (>10%)	3ml (clear) (>3.3%)	20ml (unclear) (<0.5%)
8)Isopropyl Myristate	5ml (unclear) (pH1.0)	3ml (clear) (>3.3%)	25ml (unclear) (<0.4%)	20ml (unclear) (<0.5%)	20ml (unclear) (<0.5%)	20ml (unclear) (<0.5%)
9) Dipropylene glycol methyl ether (DPM)	0.5ml (clear) (pH1.0)	1ml (clear) (>10%)	20ml (unclear) (<0.5%)	3ml (clear) (>3.3%)	8ml (clear) (>1.25%)	20ml (unclear) (<0.5%)

	α-CD (0.01g)	β-CD (0.01g)	γ-CD (0.01g)	Hydroxypropyl β-CD(0.01g)
1)Propylene Glycol	5ml (unclear) (<0.2%)	1ml (clear) (>1%)	10ml (unclear) (<0.1%)	1ml (clear) (>1%)
2)Benzyl alcohol	5ml (unclear) (<0.2%)	5ml (unclear) (<0.2%)	10ml (unclear) (<0.1%)	1ml (clear) (>1%)
3)Glycerin Formal	5ml (unclear) (<0.2%)	5ml (unclear) (<0.2%)	10ml (unclear) (<0.1%)	1ml (clear) (>1%)
4)Diethylene glycol monoethyl ether (DGMEE)	5ml (unclear) (<0.2%)	10ml (unclear) (<0.1%)	10ml (unclear) (<0.1%)	5ml (clear) (>0.2%)
5)Diethylene glycol n-butyl ether (DGBE)	5ml (unclear) (<0.2%)	10ml (unclear) (<0.1%)	10ml (unclear) (<0.1%)	5ml (clear) (>0.2%)
6)Capmul MCM	5ml (unclear) (<0.2%)	10ml (unclear) (<0.1%)	10ml (unclear) (<0.1%)	10ml (clear) (>0.1%)
7)Isopropyl alcohol (IPA)	5ml (unclear) (<0.2%)	10ml (unclear) (<0.1%)	10ml (unclear) (<0.1%)	3ml (clear) (>0.33%)
8)Isopropyl Myristate	5ml (unclear) (<0.2%)	10ml (unclear) (<0.1%)	10ml (unclear) (<0.1%)	10ml (unclear) (<0.1%)
9) Dipropylene glycol methyl ether (DPM)	5ml (unclear) (<0.2%)	10ml (unclear) (<0.1%)	10ml (unclear) (<0.1%)	5ml (clear) (>0.2%)

	EDTA	EDTA-2Na	BHT (0.1g)	BHA (0.1g)
Diethylene glycol monoethyl ether (DGMEE)	0.0026g/20ml (unclear) (<0.01%)	0.0025g/20ml (unclear) (<0.01%)	5ml (clear) (>2%)	5ml (clear) (>2%)
Diethylene glycol n-butyl ether (DGBE)	0.0021g/20ml (unclear) (<0.01%)	0.0022g/20ml (unclear) (<0.01%)	5ml (clear) (>2%)	5ml (clear) (>2%)
Dipropylene glycol methyl ether (DPM)	0.0021g/20ml (unclear) (<0.01%)	0.0021g/20ml (unclear) (<0.01%)	5ml (clear) (>2%)	5ml (clear) (>2%)

2. Formulation

	R1-1	R1-2	R1-3	R1-4	R1-5	R1-6	R1-7	R1-9
Lev.base	25.0g	25.0g	25.0g	25.0g	25.0g	25.0g		25.0g
Propylene Glycol	to 100ml	--	--	--	--	--		--
Benzyl alcohol	--	to 100ml	--	--	--	--		--
Glycerin Formal	--	--	to 100ml	--	--	--		--
DGMEE	--	--	--	To 100ml	--	--		--
DGBE	--	--	--	--	to 100ml	--		--
Capmul MCM	--	--	--	--	--	to 100ml		--
IPA	--	--	--	--	--	--	to 100ml	
DPM								to 100ml (not very clear)

DGME

E: Diethylene glycol monoethyl ether; DGBE: Diethylene glycol n-butyl ether; IPA: Isopropyl alcohol; DPM: Dipropylene glycol methyl ether.

	R2-2	R2-3	R2-4	R2-5a	R2-5b	R2-9
Amamectin	20.0g	8.0g	4.8g	8.0g	6.0g	6.0g
Benzyl alcohol	to 100ml	--	--	--	--	--
Glycerin Formal	--	to 100ml	--	--	--	--
DGMEE	--	--	to 100ml	--	--	--
DGBE	--	--	--	to 100ml (not very clear)	to 100ml	--
DPM	--	--	--	--	--	to 100ml (not very clear)

DGMEE: Diethylene glycol monoethyl ether; DGBE: Diethylene glycol n-butyl ether; IPA: Isopropyl alcohol; DPM: Dipropylene glycol methyl ether

	R3	R4	R5	R6
Lev.base	20.0g	15.0g	20.0g	20.0g
Lev.HCl	--	5.0g	--	--
Aba	1.0g	1.0g	1.0g	1.0g
β-CD	0.5g	--	--	--
Benzoic acid	--	--	5.0g	--
Citric acid	--	--	--	3.0g
Propylene Glycol	40ml	40ml	--	--
Glycerin Formal	30ml	30ml	--	--
Capmul MCM	--	to 100ml	--	--
DGBE	to 100ml	--	to 100ml	to 100ml

DGBE: Diethylene glycol n-butyl ether

	R7	R8	R9	R10	R11-1	R11-2	R12	R13	R14	R15
Lev.base	20.0g	20.0g	20.0g	20.0g	20.0g	20.0g	20.0g	20.0g	20.0g	20.0g
Aba	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g
TEA	--	--	--	1.0ml	--	--	1.0ml	1.0ml	--	--
EDTA	--	--	--	--	0.01g	--	0.01g	0.01g	0.01g	0.01g
EDTA-2Na	--	--	--	--	--	0.01g	--	--	--	--
BHT	--	--	--	--	2.0g	2.0g	2.0g	--	2.0g	--
BHA	--	--	--	--	--	--	--	2.0g	--	2.0g

Benzoic acid	--	--	--	--	--	--	--	--	5.0g	5.0g
DGMEE	to 100 ml	--	--	to 100 ml	to 100 ml	to 100 ml	to 100 ml	to 100 ml	to 100 ml	to 100 ml
DGBE	--	to 100 ml	--	--	--	--	--	--	--	--
DPM	--	--	to 100 ml	--	--	--	--	--	--	--

TEA: Triethylamine; EDTA: Ethylenediaminetetraacetic acid; BHT: Butylated Hydroxy Toluene; BHA: Butylated Hydroxyanisole; DGMEE: Diethylene glycol monoethyl ether; DGBE: Diethylene glycol n-butyl ether; DPM: Dipropylene glycol methyl ether

3. Stability results

		0 day	10days/60°C	20days/60°C	30days/60°C
R1-1 Lev.base		100%	98.1%	100.4%	100.2%
R1-2 Lev.base		100%	96.4% (a lot of degradation peaks)	83.9%	62.5%
R1-3 Lev.base		100%	98.6%	99.8%	99.4%
R1-4 Lev.base		100%	99.9%	99.6%	99.6%
R1-5 Lev.base		100%	99.7%	99.9%	99.8%
R1-6 Lev.base		100%	99.9%	99.7%	99.8%
R1-7 Lev.base		100%	99.9%	100.2%	100.6%
R1-9 Lev.base		100%	98.4%	100.0%	98.9%
R2-2 Abamectin		100%	95.2% (a lot of degradation peaks)	87.2%	90.6%
R2-3 Abamectin		100%	105.0% (?)	108.0% (?)	90.8% (?)
R2-4 Abamectin		100%	96.6%	97.6%	96.1%
R2-5a Abamectin		100%	97.7%	91.1% (?)	99.8%
R2-5b Abamectin		100%	100.1%	99.8%	111.7% (?)
R2-9 Abamectin		100%	8.9%	86.7%	91.7% (?)
R3	Lev.base	100%	99.5%	100.9%	100.9% (?)
	Aba	100%	58.7%	86.6%	37.8%
R4	Lev.base	100%	99.7%	98.8%	98.4%
	Aba	100%	58.6%	55.5%	24.0%
R5	Lev.base	100%	99.5%	90.6%	70.0%
	Aba	100%	76.2%	49.5%	42.7%
R6	Lev.base	100%	98.9%	69.5%	52.4%
	Aba	100%	70.9%	64.7%	68.2% (?)
R7	Lev.base	100%	101.1%	100.6%	100.4%

	Aba	100%	60.5%	56.3%	26.6%
R8	Lev.base	100%	99.9%	100.1%	101.0%
	Aba	100%	64.2%	58.9%	40.4%
R9	Lev.base	100%	101.4%	100.2%	98.8%
	Aba	100%	60.1%	56.1%	46.9%
R10	Lev.base	100%	94.0%	99.3%	101.7%
	Aba	100%	52.0%	47.5%	25.6%
R11-1	Lev.base	100%	101.7%	99.2%	98.3%
	Aba	100%	67.0%	60.2%	27.3%
R11-2	Lev.base	100%	106.9% (?)	100.1%	97.8%
	Aba	100%	69.3%	65.1%	38.8%
R12	Lev.base	100%	97.0%	98.8%	100.1%
	Aba	100%	53.0%	53.5%	28.5%
R13	Lev.base	100%	94.9%	99.8%	99.8%
	Aba	100%	53.5%	55.5%	28.2%
R14	Lev.base	100%	64.5% (a lot of degradation peaks)	89.4% (?)	70.6%
	Aba	100%	56.1%	58.4%	23.7%
R15	Lev.base	100%	79.7% (a lot of degradation peaks)	96.0% (?)	82.9%
	Aba	100%	67.6%	58.9%	30.2%

4. Discussion

1) The contents of Lev.base in R1 (10, 20 and 30days/60°C) were as follows: R1-1 (98.1%, 100.4% and 100.2% in Propylene glycol), R1-2 (96.4%,83.9% and 62.5% in Benzyl alcohol). R1-3 (98.6%, 99.8% and 99.4% in Glycerol formal), R1-4 (99.9%, 99.6% and 99.6% in DGMEE), R1-5 (99.7%, 99.9% and 99.8% in DGBE), R1-6 (99.9%, 99.7% and 99.8% in Capmul MCM), R1-7 (99.9%, 100.2% and 100.6% in IPA), R1-9 (98.4%, 100.0% and 98.9% in DPM). R1-2 is the worst in terms of stability. The content of Lev.base is between 98.4%~100.6%. It shows that Benzyl alcohol is not a suitable solvent for Lev.base.

2) The contents of Abamectin in R2 (10, 20 and 30 days/60°C) were as follows: R2-2 (95.2%, 87.2% and 90.6% in Benzyl alcohol), R2-3 (105.0%, 108.0% and 90.8% in Glycerol formal), R2-4 (96.5%, 97.6% and 96.1% in DGMEE), R2-5a (97.7%, 91.1% and 100.0% in DGME, the concentration of Abamectin is 8%), R2-5b (100.1%, 99.9% and 111.7% in DGME, the concentration of Abamectin is 6%), R2-9 (81.9%, 86.7% and 91.7% in DPM).

3) The contents of Lev.base and Abamectin (10, 20 and 30days/60°C) were (99.5%, 58.7%), (100.9%, 36.5%) and (100.9%, 37.8%) in R3 [(20%Lev.base + 1%Aba + 0.5%β-CyD) / (40%Propylene glycol + 30%Glycerin formal +DGME)]. The contents of Lev.base and Abamectin were (99.7%, 58.6%), (98.8%, 35.5%) and (98.4%, 24.0%) in R4 [(15%Lev.base + 5%Lev.HCl + 1%Aba) / (40%Propylene glycol + 30%Glycerin formal +DGME)]. Lev.base was stable in both of R3 and R4. But Abamectin had a significant degradation in R3 and R4. The results showed that the stability of Abamectin can not be improved after β-CyD or Lev.HCl were added into formulation; the mixture of (P.G+G.F+DGME) is not a good solvent for (Lev.base+Aba) Pour on.

4) The contents of Lev.base and Abamectin (10, 20 and 30days/60°C) were (99.5%, 76.2), (90.6%, 49.5%) and (70.0%, 42.7%) in R5 [(20%Lev.base + 1%Abamectin + 5%Benzoic acid)/DGME]. The result showed that abamectin became more stable, Lev.base became unstable after 5% of Benzoic acid was added into formulation; DGBE was a suitable solvent for Lev.base and Abamectin.

5) The contents of Lev.base and Abamectin (10, 20 and 30days/60°C) were (98.9%, 70.9%), (69.5%, 64.7) and (52.4, 69.4%) in R6 [(20%Lev.base + 1%Abamectin + 3%Citric acid)/DGBE]. The result demonstrated that abamectin became more stable, Lev.base became unstable after 3% of Citric acid was added into formulation (3% is the highest concentration of citric acid which may be used according to the result of previous solubility study).

6)The contents of Lev.base and Abamectin (10, 20 and 30days/60°C) were (101.1%, 60.6%), (100.6%, 36.5%) and (100.4%, 26.6%) in R7 (20%Lev.base + 1%Aba/DGMEE), (99.9%, 64.2%), (101.0%, 52.9%) and (101.0%, 40.4%) in R8 (20%Lev.base + 1%Aba/DGBE), (101.4%, 60.1%), (100.2%, 55.4%) and (98.8% 46.9%) in R9 (20%Lev.base + 1%Aba/DPM). The results showed that abamectin was more stable in DGBE. DPM also was good solvent for Lev.base & Abamectin pour on.

7) The contents of Lev.base and Abamectin (10, 20 and 30days/60°C) were (94.0%, 52.0%), (99.3%, 37.5%) and (101.7%, 25.6%) in R10 (20%Lev.base + 1%Aba + 1%TEA/DGMEE). Compared with (101.1%, 60.6%), (100.6%, 36.5%) and (100.4%, 26.6%) in R7 (20%Lev.base + 1%Aba/DGMEE). There was no significant difference in the stability of

Lev.base & abamectin in R10 and R&. It seems that TEA had no effect on the stability of actives.

8) The contents of Lev.base and Abamectin (10, 20 and 30days/60°C) were (101.7%, 67.0%). (99.2%, 40.2%) and (98.3, 27.3%) in R11-1 (20%Lev.base + 1%Aba + 0.01%EDTA +2%BHT/DGMEE) and (106.9%, 63.3%). (100.1%, 57.1), (97.8%, 38.8) in R11-2 (20%Lev.base + 1%Aba + 0.01%EDTA-2Na + 2%BHT/DGMEE) separately. Abamectin was more stable in R11-2 than in R11-1. The stability of Lev.base had no significant difference between R11-1 (EDTA) and R11-2 (EDTA-2Na). Compared with R7 (20%Lev.base+1%Aba/DGMEE), no improvement was found in the stability of Abamectin after EDTA or EDTA-2NA and BHT were added into formula. But compared with R14 (20%Lev.base + 1%Abamectin + 5%Benzoic acid + 0.01%EDTA + 2%BHT/DGMEE), the results showed that the stability of actives became worse when 5%Benzoic acid, 0.01%EDTA and 2%BHT were added into formula. It seems that EDTA and BHT should not be used at the same time with Benzoic acid. Usual usage concentration of EDTA and EDTA-2Na is 0.0005%~0.02%.

9) The contents of Lev.base and Abamectin (10, 20 and 30days/60°C) were (97.0%, 53.0%), (98.8%, 33.5%), (100.1%, 28.3%) in R12 (20%Lev.base + 1%Aba + 1%TEA + 0.01%EDTA + 2%BHT). The stability of Lev.base and Abamectin had no significant difference compared with R11-1 or R11-2.

10) The stability of Lev.base and Abamectin had no significant difference in R12 (20%Lev.base + 1%Aba + 1%TEA + 0.01%EDTA + 2%BHT) and R13 (20%Lev.base + 1%Aba + 1%TEA + 0.01%EDTA + 2%BHA).

11) The contents of Lev.base and Abamectin (10, 20 and 30days/60°C) are (64.5%, 56.1%), (89.4%, 38.4%), (70.6%, 23.7%) in R14 (20%Lev.base + 1%Aba + 5%Benzoic acid + 0.01%EDTA + 2%BHT/DGMEE) and (79.7%, 67.6%), (96.0%, 38.9%), (82.9%, 30.2%) in R15 (20%Lev.base + 1%Aba + 5%Benzoic acid + 0.01%EDTA + 2%BHA/DGMEE).

Study 8

1. Formulation (BN: 071201)

	F1 (R5)	F2 (R10)	F3 (R16)	F4 (R17)	F5 (R18)	F6 (R19)	F7 (R11-1)	F8 (R20)
Lev.base	20.0g	20.0g	20.0g	20.0g	20.0g	20.0g	20.0g	20.0g
Abamectin	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g
TEA	--	1.0ml	1.0ml	--	1.0ml	1.0ml	--	--
EDTA	--	--	--	--	--	--	0.01g	0.01g
H_2O	--	--	--	10g	10g	10g	--	10g
BHT	--	--	--	--	--	--	2.0g	2.0g
BHA	--	--	--	--	--	--	--	--
Benzoic Acid	5.0g	--	5.0g	5.0g	--	5.0g	--	--
DGMEE to	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml

TEA: Triethylamine; EDTA: Ethylenediaminetetraacetic acid; BHT: Butylated Hydroxy Toluene; BHA: Butylated Hydroxyanisole; DGMEE: Diethylene glycol monoethyl ether

2. Stability results (Mobile phase: ACN-H_2O-Ammonia: 80:20:0.1,V/V)

		0 day	10 days/60°C	20 days/60°C	30 days/60°C
F1 (R5)	Lev.base	100% (415307)	99.6%	78.3%	63.8%
	Aba	*100% (23725)*	*69.5%*	*58.5%*	*30.3%*
F2 (R10)	Lev.base	100% (412086)	100.3%	100.3%	104.6% (?)
	Aba	*100% (22487)*	*73.7%*	*50.2%*	*27.2%*
F3 (R16)	Lev.base	100% (411304)	99.7%	99.9%	87.7%
	Aba	*100% (27067.?)*	*52.3%*	*49.8%*	*26.9%*
F4 (R17)	Lev.base	100% (409190)	34.4%	9.2% (?)	8.2% (?)
	Aba	*100% (23531)*	*64.0%*	*52.8%*	*46.1%*
F5 (R18)	Lev.base	100% (408015)	100.2%	97.2%	47.7%
	Aba	*100% (26909.?)*	*32.7%*	*No peak*	*No peak*
F6 (R19)	Lev.base	100% (405210)	47.9%	40.1%	34.5%
	Aba	*100% (20699)*	*63.2%*	*55.5%*	*45.4%*
F7 (R11-1)	Lev.base	100% (404309)	100.1%	99.0%	102.6%
	Aba	*100% (20192)*	*72.6%*	*67.6%*	*53.9%*
F8 (R20)	Lev.base	100% (404448)	100.3%	99.3%	98.1%
	Aba	*100% (19600)*	*53.6%*	*26.8% (?)*	*No peak*

2. Discussion

1) Lev.base degraded quickly with the existence of benzoic acid (F1 or R5 in study7).

2) In F2 (R10 in study7, containing TEA), Lev.base had no degradation.

3) The content of Lev.base in F3 (R16 in study7, containing TEA and Benzoic acid) is lower than that in F2. The content of Abamectin in F3 has no difference compared with that in F2. It seems that TEA (alkali) is good additive for Lev.base.

4) Lev.base degraded very quickly in F4 (R17 in study7, containing H_2O and Benzoic acid).

5) Abamectin degraded very quickly in F5 (R18 in study7, containing H_2O and TEA).

6) In F6 (R19 in study7, containing H_2O, TEA and Benzoic acid), the content of Lev.base is very low. It hints acid and water are very bad for Lev.base.

7) In F7 (R11-1 in study7, containing EDTA and BHT), the contents of Lev.base and Abamectin are (100.1%, 72.6%), (99.0%, 67.6%) and (102.6%, 53.9%). EDTA and BHT have no great effects on stability of Lev.base and Abamectin.

8) Water is very bad for the stability of Abamectin (F8 or R20 in study7, containing EDTA, BHT and H_2O).

Study 9

1. Formulation (BN: 201201)

	R1	R2	R3	R4	R5	R6
Lev.base	20.0g	20.0g	20.0g	20.0g	20.0g	20.0 g
Abamectin	1.0g	1.0g	1.0g	1.0g	1.0g	1.0g
Benzoic Acid	5.0g	5.0g	5.0g	10.0g	--	--
Acetic acid	--	--	--	--	2.0ml	4.0ml
BHA	--	--	2.0g	--	--	--
DGMEE to	100ml	--	--	--	--	--
DGBE to	--	100ml	100ml	100ml	100ml	100ml

BHA: Butylated Hydroxyanisole; DGMEE: Diethylene glycol monoethyl ether; DGBE: Dithylene glycol n-butyl ether

2. Stability results (Mobile phase: ACN-H_2O-Ammonia: 80:20:0.1,V/V)

		0 day	10 days/60°C	20 days/60°C	30 days/60°C*
R1	Lev.base	100%	105.8% (?)	85.5%	79.4%
	Aba	*100%*	*58.1%*	*32.2%*	*31.0%*
R2	Lev.base	100%	98.9%	73.9%	68.4%
	Aba	*100%*	*74.7%*	*49.5%*	*45.6%*
R3	Lev.base	100%	98.5%	73.5%	61.2%
	Aba	*100%*	*83.8%*	*57.2%*	*50.8%*
R4	Lev.base	100%	90.7%	69.0%	50.6%
	Aba	*100%*	*83.0%*	*58.2%*	*40.6%*
R5	Lev.base	100%	100.0%	99.1%	100.4%
	Aba	*100%*	*76.0%*	*48.5%*	*28.4%*
R6	Lev.base	100%	99.8%	99.6%	99.3%
	Aba	*100%*	*85.6%*	*57.7%*	*57.1%(?)*

*The temperature in oven was changed into 55°C after stored for 20days.

3. Discussion

1) Lev.HCl is more stable in DGMEE than in DGBE. Abamectin is more stable in DGBE than in DGMEE.

2) BHA had no significant effect on the stability of Lev.HCl and Abamectin.

3) Lev.HCl had high degradation with existence of 10% of benzoic acid.

4) The formulation and analysis of R5 and R6 should be repeated.

Study 10 (The effect of excipient)

1. Formulation (BN:111201)

	R1	R2	R3
Benzoic acid	5.0g	--	--
BHT	--	5.0g	--
BHA	--	--	5.0g
DGBE to	100 ml	100 ml	100 ml

Study 11 (BN: 280102)

1. Formulation

	R1	R2	R3	R4	R5
Lev.base	20.0 g	20.0 g	20.0 g	20.0 g	20.0 g
Abamectin	1.0 g	1.0 g	1.0 g	1.0 g	1.0 g
Acetic acid	--	2.0 ml	4.0 ml	6.0 ml	10.0 ml
*DGBE to	100 ml	100 ml	100 ml	100 ml	100 ml

*DGBE: Diethylene glycol n-butyl ether

2. Stability results

		0 day	10 days/60°C	20 days/60°C	30 days/60°C
R1	Lev.base	100%	99%	97%	96%
	Aba	100%	83%	79%	52%
R2	Lev.base	100%	82%	67%	50%
	Aba	100%	66%	57%	51%
R3	Lev.base	100%	78%	60%	40%
	Aba	100%	77%	67%	55%
R4	Lev.base	100%	52%	46%	23%
	Aba	100%	88%	85%	75%
R5	Lev.base	100%	55%	46%	19%
	Aba	100%	85%	67%	55%

4. Discussion

Acetic acid did not affect the stability of Abamectin. However, the stability of Lev.base has been significantly affected.

Study 12 (BN: 060302)

1. Formulation

	R1	R2	R3	R4	R5	R6	R7	R8
Lev.base	--	--	--	--	25 g	25 g	25 g	25 g
Abamectin	6 g	8 g	6 g	8 g	--	--	8 g	8 g
DGMEE to	100ml	100ml	--	--	100ml	--	100ml	--
DGBE to	--	--	100ml	100ml	--	100ml	--	100ml

R9	R10	R11	R12
15%R2 + 85%R5	15%R2 + 85%R6	15%R4 + 85%R5	15%R4 + 85%R6

2. Stability results

		0 day	14 days/55°C	14 days/55°C
R1	Lev.base	--	--	--
	Abamectin (6%)	*100%*	*97%*	*92%*
R2	Lev.base	--	--	--
	Abamectin (8%)	*100%*	*96%*	*98%*
R3	Lev.base	--	--	--
	Abamectin (6%)	*100%*	*80%*	*75%*
R4	Lev.base	--	--	--
	Abamectin (8%)	*100%*	*98%*	*98%*
R5	Lev.base (25%)	100%	97%	97%
	Abamectin			
R6	Lev.base (25%)	100%	94%	92%
	Abamectin			
R7	Lev.base (25%)	100%	94%	93%
	Abamectin (8%)	*100%*	*72%*	*57%*
R8	Lev.base (25%)	100%	95%	85%
	Abamectin (8%)	*100%*	*70%*	*49%*
R9	Lev.base (20%)	100%	99%	96%
	Abamectin (1.2%)	*100%*	*92%*	*90%*
R10	Lev.base (20%)	100%	95%	95%
	Abamectin (1.2%)	*100%*	*73%*	*52%*
R11	Lev.base (20%)	100%	97%	95%
	Abamectin (1.2%)	*100%*	*70%*	*70%*
R12	Lev.base (20%)	100%	96%	95%
	Abamectin (1.2%)	*100%*	*75%*	*55%*

Study 13 Abamectin and Levamisole Base in n-methyl Pyrrolidone

A trial was carried out using N-Methyl-2-Pyrollidone (Pharmasolv) as the base solvent. Three formulations were prepared:

(a) 5.75% w/v Abamectin in Pharmasolv.

(b) 25% w/v Levamisole in Pharmasolv.

(c) A combination of 1.15 w/v Abamectin and 20% w/v Levamisole in Pharmasolv.

Three of the DGBE formulations preferred from the previous experiments were also prepared for the purposes of comparative evaluation:

(a) 5.75% w/v Abamectin in DGBE.

(b) 25% w/v Levamisole in DGBE.

(c) A combination of 1.15 w/v Abamectin and 20% w/v Levamisole in DGBE.

All the formulations were kept at 60°C and were analysed to assess the extent of degradation after (0,3,7 & 14) days.

The results are presented in the following table. The main results of this experiment were:

- there was no significant difference in the extent of degradation samples in DGBE or Pharmasolv when abamectin or levamisole are present alone in the solution.
- There was significant degradation of abamectin after 7 days in DGBE base when levamisole and abamectin are present together. There was almost insignificant degradation of Levamisole in the combination sample in DGBE.

The stability results of the solution containing both the actives in Pharmasolv demonstrated that surprisingly a pyrollidone base was capable of stabilizing both of these very incompatible actives. There was no significant degradation of Levamisole or Abamectin even after 14 days at 60°C.

Sample Name	Abamectin – 5.75% w/v (% of label claim)	Levamisole – 25% w/v (% of label claim)	Abamectin content in combination solution – 1.15% w/v (% of label claim)	Levamisole content in combination solution – 20% w/v (% of label

				claim)
In DGBE base	95.83	94.96	94.78	97.90
3 days at 60°C (DGBE base)	102.78	87.48	88.70	98.35
7 days at 60°C (DGBE base)	102.61	88.20	76.52	98.25
In Pharmasolv base	105.57	102.72	97.39	100.85
3 days at 60°C (Pharmasolv)	97.39	101.60	96.52	100.25
7 days at 60°C (Pharmasolv)	109.91	99.76	94.78	99.95
14 days at 60°C (Pharmasolv)	104.17	95.40	93.91	96.30

PREFERRED EMBODIMENT

The preferred formulations of the invention therefore include avermectin or milbemycin in combination with levamisole or morantel and a solvent selected from the pyrollidone group. The pyrollidone group includes the following members n-methyl-2-pyrrolidone, n-methyl pyrrolidone, 2-pyrrolidone. In particular N-methyl-2-pyrrolidone sold as Pharmasov has been found to be useful in the preparation of the formulations of the present invention.

As a result of the findings in the above investigation, it was decided to use pyrrolidone as a base for levamisole/avermectin formulations.

The following examples are provided as examples only and are in no way intended to limit the spirit or scope of the invention.

Sample Formulations

Topical Formulations

Example of topically applied formulations of the invention include:

Formulation 1.

Ingredient	% w/v
Abamectin	1%
Levamisole Base	20%
n-methyl pyrrolidone	q.v.

Formulation 2.

Ingredient	% w/v
Ivermectin	0.5%
Levamisole Base	10%
n-methyl pyrrolidone	q.v.

Examples of Injectable formulations include:

Formulation 1.

Ingredient	% w/v
Ivermectin	0.5%
Levamisole Phosphate	20%
2- pyrrolidone	q.v.

Formulation 2.

Ingredient	% w/v
Moxidectin	0.5%
Levamisole Phosphate	20%
2 - pyrrolidone	q.v.

Examples of Orally administered formulations include:

Formulation 1.

Ingredient	% w/v
Abamectin	0.1%
Levamisole Base	5%
n-methyl pyrrolidone	q.v.

Formulation 2.

Ingredient	% w/v
Ivermectin	1%
Levamisole Base	5%
n-methyl pyrrolidone	q.v.

Formulation 3.

Ingredient	% w/v
Abamectin	1%
Levamisole Base	20%
n-methyl pyrrolidone	q.v.

Formulation 4.

Ingredient	% w/v
Abamectin	1%
Levamisole Base	20%
n-methyl pyrrolidone	q.v.

Formulation 5.

Ingredient	% w/v
Abamectin	1%
Levamisole Base	20%
n-methyl pyrrolidone	q.v.

Those skilled in the art will appreciate that dose rates for these formulations are generally in the order of 1ml to 5kg to 1ml per 20kg for oral administration, 1ml per 25 kg or 1ml per 50kg for administration by injection, and 1ml per 10kg or 1ml per 20kg for topical administration.

ADVANTAGES

The present invention is advantageous as it allows simultaneous both avermectin and levamisole to an animal.

It solves the problems raised in the background without resorting to complex multiphasic formulations.

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